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10/505,191	06/24/2005	Jeffrey P. Erickson	AIB-09206	5158

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,191	ERICKSON, JEFFREY P.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-29,32-35 and 41-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 15-29, 32-35, 41-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 10/0107 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-13, 15-29, 32-35, 41-56 are pending and under consideration. Claims 14, 30-31, 36-40 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15-29, 32-35, 41-56 as amended or newly added remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting transcription control region in salivary gland cells, does not reasonably provide enablement for a transgenic non-human mammal by way of the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic non-human mammal expressing a polypeptide in saliva at a level of at least 0.5 mg/ml, a method of collecting saliva from the same transgenic non-human mammal, and a method of producing the same transgenic non-human mammal.

The specification has asserted that the invention features transgenic non-human mammals that express transgenic polypeptides in their saliva. The specification discusses that salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest. See pages 26-28 of the specification. However, the

guidance provided by the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals embraced by the claims. Moreover, the guidance provided by the specification is general as it does not even disclose which saliva regulatory elements could be used to create any of the transgenic non-human mammals embraced by the claims. Finally, the working examples provided by the specification (see pages 81-101) while exemplifying creation of different transgenic cows that express prothrombin and fibrinogen in their saliva respectively, did not disclose which saliva regulatory elements were used to create the transgenic cows and therefore failed to provide the skilled artisan with adequate guidance to make any of the transgenic non-human mammals embraced by the claims. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a first issue, the claims embrace transgenic non-human mammals that express and produce a transgenic polypeptide in saliva. The specification has discussed that saliva specific regulatory elements are necessary to achieve expression of a polypeptide of interest in saliva of a transgenic non-human mammal. See pages 26-29 of the specification. However, the guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (PSP and B1-Ips genes) (p 27-28) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217,

which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson. Finally, in an attempt to provide guidance as to which saliva regulatory sequence may be used within the scope of the claimed invention, the specification has relied on improper incorporation by reference of subject matter that appears to be essential. See the references to Mikkelsen, Larson and Mirels at pages 27-28 of the specification. Applicant is reminded that subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. See 37 C.F.R. 1.57(c) and MPEP 608.01(p). Accordingly, given the lack of guidance provided by the specification, the skilled artisan would not know which regulatory sequence to use to achieve saliva specific expression of a polypeptide in a transgenic non-human mammal. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use any of the transgenic non-human mammals embraced by the claims without a reasonable expectation of success.

As a second issue, while the claims embrace transgenic non-human mammals expressing a transgenic polypeptide in saliva, the working examples provided by specification did not provide adequate guidance that would enable one of skill in the art to create any of the transgenic non-human mammals embraced by the claims. The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva. However, the working examples failed to disclose which saliva regulatory elements were used in the creation the transgenic cows. As previously stated the specification as a whole has not even identified or provided the regulatory elements necessary to practice the claimed invention. A mere statement that saliva regulatory elements existed and could be used is not sufficient to enable the breadth of the claims as

directed to transgenic non-human mammals expressing transgenic polypeptides in saliva. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. The art teaches that parotid-specific transgene expression requires an upstream cis-regulatory domain, namely the parotid control region, and this parotid control region functions with a heterologous promoter and is indispensable for achieving transgene expression and deletion of specific regions results in ectopic gene expression and the inducible expression of the transgene expression in transgenic mice decreases over 30-fold (abstract) (**Tu et al**, Gene Expr, 3(3): 289-305, 1993). In this case the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims. Given, the lack of guidance and absence of working examples provided by the specification correlating to creation of transgenic non-human mammals, the lack of guidance provided by the specification with respect to use of saliva regulatory elements, the unpredictability of saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Applicants argue that the data presented in "The Erickson Declaration" demonstrate that a mammal (i.e., for example, a female goat or dam) fibroblast can be transfected with a plasmid vector comprising an exogenous protein and using the transfected fibroblast in somatic cell nuclear transfer techniques thereby giving birth to a doe that expresses the transgene and secretes the exogenous protein into saliva. In this case, the exogenous protein was human serum albumin (hSA) whose nucleic acid (as well as the promoter nucleic acid) was identified in epithelial skin samples of the transgenic doe. Applicants argue that the promoter construct

utilized in the transfection comprises a bovine salivary protein gene (i.e., for example, bSP30a) which is a major salivary protein having the following exemplary support in the Applicants' specification on page 27 where it is recited "In particular in this regard, expression control regions from the gene for parotid secretory proteins ("PSP") generally are suitable to engineer salivary-gland specific gene expression, in the manner Mikkelsen and so-workers used control regions from the gene for mouse PSP ("moPSPW) to engender parotid-specific transgenic expression in mice. ... The general organizational schema of the transcription control regions necessary and sufficient for specific and efficient transgenic expression in salivary gland cells in mice fits the general organizational model of transcription control regions of other genes with tissue-specific patterns of expression." Applicants argue accordingly, in view of this recitation the PSP paradigm for salivary gland- specific expression in mice can be followed to isolate the genetic elements for efficient, salivary gland-specific expression in other animals Applicant's Specification, pg 27 In 6-29. Applicants argue that have provided details of both promoter construction as well as the necessary polymerase chain reaction primers in The Erickson Declaration, Figures 1-3 and ¶ 3-4.

These arguments are not persuasive because at the time of filing the specification fails to correlate the endogenous expression of BSP3a and BSP30b to exogenous expression of BSP30a and BSP30b in a non-human mammal's saliva producing 0.5 mg/ml of a polypeptide as claimed in the instant application. While the Erickson declaration describes the expression of both BSP30a and BSP30b is restricted to salivary gland tissue, however the specification fails to provide guidance to an exogenous nucleic acid encoding at least one transgenic polypeptide, wherein said nucleic acid operably linked to a BSP30a or BSP30b salivary gland-specific cis-

acting transcription control regions, wherein said polypeptide is produced in a non-human mammal's saliva at a level of at least 0.5 mg/ml as claimed in the instant application.

The citation in the specification, p 27 that expression control regions from the gene for parotid secretory proteins ("PSP") are suitable to engineer salivary-gland specific gene expression, in the manner Mikkelsen and so-workers used control regions from the gene for mouse PSP ("moPSPW) to engender parotid-specific transgenic expression in mice, **does not** provide guidance for a BSP30a or BSP30b salivary gland-specific cis-acting transcription control regions. Moreover, the transgenic goat as disclosed in the Erickson declaration does not disclose the production of the polypeptide is produced in saliva at a level of at least 0.5 mg/ml as claimed in the instant application. As discussed in the previous office action mailed 3/26/07 pages 6-8 for example, ".....Applicants have not disclosed what are the regulatory sequences necessary to achieve saliva specific expression of a polypeptide of interest in a transgenic mammal at the claimed levels. Applicants have not correlated the use of parotid gland expression cassette, carrying all known regulatory regions in the Psp gene to the expression of a heterologous protein in the saliva of a transgenic mammal to overcome the art limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene as discussed by Samuelson. Applicants have not disclosed the main regulatory region or enhancer in the murine PSP gene to achieve the expression of a claimed polypeptide in a transgenic mammal. Note the specification recognizes the importance of regulatory sequences, in addition to the promoter sequences such as enhancers, splice signals, transcription termination signals and polyadenylation sites,

among others which are useful regulatory sequences that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms." (see specification p 34).....Applicant is reminded that the subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. The MPEP states § 1.57 Incorporation by reference:

> "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:
> (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112;"

Note the specification points to the importance of the regulatory sequences besides the promoter for the claimed invention by emphasizing: "Among the sequences that regulate transcription that are useful in the invention, in addition to the promoter sequences discussed above, are enhancers, splice signals, transcription termination signals and polyadenylation sites, among others. Particularly useful regulatory sequences include those that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms. Also particularly preferred in this regard are those that increase the specificity of expression in targeted compartments of a transgenic organism. Among highly particularly preferred regulatory regions in this regard are those that increase the efficiency, the specificity or both the efficiency and the specificity of expression in salivary glands, and the production of a desired substance thereby in the saliva of transgenic non-human animals in accordance with the invention." (see specification p 34-35). The guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular

regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (from PSP and B1-Ips genes) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn.**

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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